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A Review of Pneumatosis Intestinalis in the Setting of Systemic Cancer Treatments, Including Tyrosine Kinase Inhibitors

Niranjan Vijayakanthan, MD[a,*], Kavita Dhamanaskar, MD, FRCPC[b,*], Lori Stewart, MD, FRCPC[b], Jodie Connolly, RN[c], Brian Leber, MD, FRCPC[d,e], Irwin Walker, MD, FRCPC[d,e], Michael Trus, MD, PhD, FRCPC[d,f,†]

[a]*The Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada*
[b]*Department of Radiology, Juravinski Hospital, Hamilton, Ontario, Canada*
[c]*Department of Nursing, Hamilton General Hospital, Hamilton, Ontario, Canada*
[d]*Division of Hematology, Hamilton Health Sciences, Hamilton, Ontario, Canada*
[e]*Department of Medicine, McMaster University, Hamilton, Ontario, Canada*
[f]*Department of Pathology and Molecular Medicine, Hamilton Health Sciences, Hamilton, Ontario, Canada*

Abstract

Purpose: Pneumatosis intestinalis is a radiologic diagnosis that manifests in a variety of clinical settings. We report 4 cases of pneumatosis intestinalis in patients undergoing cancer treatments that included cytotoxic agents and/or tyrosine kinase inhibitors. These reports aim to provide insight into the clinical interpretation and pathogenesis of pneumatosis intestinalis in the setting of cancer treatments and demonstrate a potential association with tyrosine kinase inhibitors.
Methods: Radiologists responsible for the interpretation of adult imaging at our tertiary care centre were surveyed to identify cases of pneumatosis intestinalis arising in the midst of cancer treatment. The case histories were reviewed by physicians with expertise in cancer treatment.
Results: Four cases of chemotherapy-related pneumatosis intestinalis were identified. The diagnosis was made in 1 patient during investigations undertaken for non–life-threatening abdominal symptoms and incidentally in 2 patients by abdominal imaging used to measure chemotherapy response. A fourth patient presented in a life-threatening manner, and abdominal imaging was symptom guided. Interestingly, 3 of the 4 patients were receiving treatments that included a tyrosine kinase inhibitor, and this agent was the only identifiable potential etiology in 1 patient.
Conclusions: The significance of pneumatosis intestinalis arising during cancer treatments is difficult to interpret because of the complex nature of the diseases and the treatments that often include combinations of cytotoxic agents and/or novel therapies. These reports demonstrate the importance of classifying this radiologic finding according clinical severity rather than etiology and underscore the need for continued observation for unexplained adverse effects when using novel therapies.

Résumé

Objectif : La pneumatose intestinale est un diagnostic radiologique qui se manifeste dans divers contextes cliniques. Nous signalons quatre cas de pneumatose intestinale chez des patients qui ont des traitements pour le cancer incluant notamment des agents cytotoxiques ou des inhibiteurs de la tyrosine-kinase. Les cas ont été signalés afin de nous aider à mieux comprendre l'interprétation clinique et la pathogénèse de la pneumatose intestinale dans un contexte de traitement du cancer, et de démontrer un lien possible avec les inhibiteurs de la tyrosine-kinase.
Méthodes : On a demandé aux radiologistes responsables de l'interprétation des examens d'imagerie pour adultes de notre centre de soins tertiaires de déceler les cas de pneumatose intestinale chez des patients en cours de traitement du cancer. Les dossiers ont été étudiés par des oncologues.
Résultats : Quatre cas de pneumatose intestinale liée à la chimiothérapie ont été décelés. Un patient a été diagnostiqué pendant l'examen de symptômes abdominaux ne mettant pas en danger la vie et deux patients ont été diagnostiqués lors d'examens effectuées afin d'évaluer la

* N.V. and K.D. contributed equally to this manuscript.
† Address for correspondence: Michael Trus, MD, PhD, FRCPC, Henderson General Hospital Site, 711 Concession St, Hamilton, Ontario L8V 1C3, Canada.

E-mail address: trus@hhsc.ca (M. Trus).

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réponse à la chimiothérapie. Un quatrième patient s'est présenté avec une affection pouvant mettre la vie en danger et l'imagerie abdominale a été effectuée en fonction des symptômes. Fait intéressant, trois des quatre patients recevaient des traitements comprenant un inhibiteur de la tyrosine-kinase et cet agent était la seule cause potentiellement définissable chez un patient.

Conclusion : Il est difficile d'interpréter l'importance clinique de la pneumatose intestinale qui se produit pendant le traitement du cancer en raison de la complexité des pathologies et des traitements, qui regroupent souvent une combinaison d'agents cytotoxiques ou de thérapies nouvelles. Les rapports démontrent l'importance de répertorier ces résultats radiologiques selon la gravité clinique plutôt que la cause, ainsi que la nécessité de continuer à observer les effets indésirables et non expliqués lors de l'utilisation de thérapies nouvelles.

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Key Words: Pneumatosis intestinalis; Cancer; Chemotherapy; Tyrosine kinase inhibitors; Review

Pneumatosis intestinalis (PI), defined as gas within the bowel wall, is a radiologic finding rather than a clinical diagnosis [1]. Treatment decisions are based on the clinical presentation rather than the radiologic finding itself. We present 4 incidences of PI that developed in patients undergoing systemic cancer treatments in which the clinical scenarios ranged from mild non–life-threatening presentations to life-threatening situations. Interestingly, 3 of the patients were receiving treatments that included tyrosine kinase inhibitors (tki) in which this relatively new class of anticancer agents target dysregulated signal transduction pathways [2]. Recent reports have implicated multitargeted tki agents in the development of PI [3,4]. However, PI has not been associated with the use of more-selective tki agents such as imatinib mesylate used in the treatments described below. The potential causes and pathogenesis of PI are discussed in relation to these clinical scenarios, and we explore the possibility that PI is a class effect of both multitargeted and selective tki agents.

Clinical Cases

Case 1

A 29-year-old man with β-thalassemia trait was diagnosed with chronic myelogenous leukaemia (CML) when he presented with a white blood cell (WBC) count of 380×10^9/L (reference range, 4-11 $\times$ 10^9/L) and splenomegaly. The patient was anemic (hemoglobin, 70 g/L), and the platelet count was normal.

Standard treatment with the selective tki imatinib mesylate 400 mg/d was initiated [5]. Twelve weeks later, the patient described 3 episodes of melena over 1 day. The abdominal examination was normal, and the patient was afebrile. The platelet and the absolute neutrophil counts were normal, as were coagulation parameters. Plain radiographs of the abdomen revealed PI within the ascending colon without free intra-abdominal air (Figure 1A). Computed tomography (CT) of the abdomen detected PI extending from the cecum to the proximal transverse colon, with collections of extraluminal gas anterior to the cecum and the ascending colon (Figure 1B).

Imatinib was discontinued, and conservative management was recommended. Blood cultures remained sterile. Plain radiographs obtained 2 weeks later showed a reduction of intramural gas. The patient underwent an unrelated allogeneic bone marrow transplantation 156 days after discontinuing imatinib and died from acute graft-versus-host disease. Serologic studies were negative for human immunodeficiency virus 1 and 2 and cytomegalovirus.

Case 2

PI was detected in a 68-year-old woman by CT imaging undertaken to measure the response of her recurrent renal cell carcinoma (RCC) to the oral tki sunitinib malate. Comorbidities included essential hypertension and chronic obstructive pulmonary disease. Intravenous contrast agent for CT was withheld because of an elevated serum creatinine. PI was seen within the distal small bowel along with free intraperitoneal air and dilated loops of bowel (Figure 2). The patient was asymptomatic and afebrile, and without peritoneal signs but described anorexia and watery diarrhoea 2 days prior. The complete blood cell count was normal, urea 21.2 mmol/L (reference range, 3.0-6.5 mmol/L), and creatinine 481 μmol/L (reference range, 50-100 μmol/L). Azotemia was related to the diarrhoea, anorexia, and prior nephrectomy. The patient was treated briefly with intravenous hydration and antibiotics, and sunitinib was discontinued. The creatinine decreased and sunitinib was resumed at a reduced dosage. CT imaging 4 months later revealed resolution of PI and RCC progression. Sunitinib was discontinued.

Case 3

PI was detected incidentally by CT imaging in a 48-year-old man with T-cell non-Hodgkin lymphoma (NHL), undertaken to measure chemotherapy response. Other medical conditions included essential hypertension and dyslipidemia. The patient originally presented with an abdominal mass and required a transverse colectomy, small bowel resection, and ileostomy when the diagnosis of NHL was confirmed. Treatment with systemic chemotherapy, which included cytotoxic agents and steroids (CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone]), was initiated. Six days after starting the fourth cycle (128 days after surgery), CT imaging showed extensive PI in the distal small bowel loops and extraluminal air anterior to the

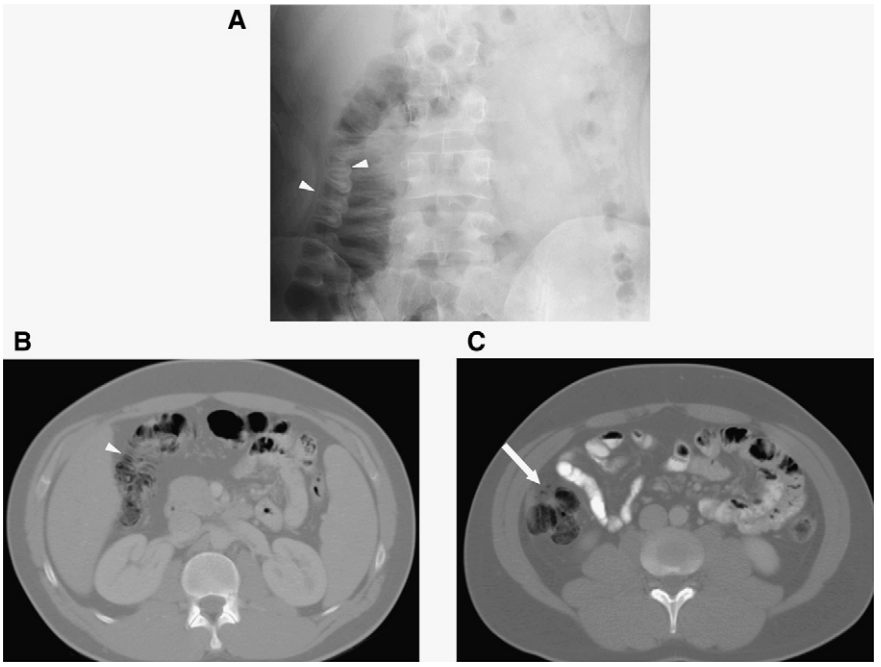

Figure 1. Pneumatosis intestinalis developing in a patient diagnosed with chronic myelogenous leukaemia 12 weeks after starting therapy with the tyrosine kinase inhibitor imatinib. (A) Left lateral decubitus plain radiograph, showing intramural gas (arrowheads) in the ascending colon. (B) Axial computed tomographic images of the abdomen confirms intramural gas in transverse and ascending colon (arrowhead). (C) Small foci of extraluminal gas (arrow) is consistent with localized perforation of the colon.

renal fascia. (Figure 3). The lymphadenopathy had improved. The patient was asymptomatic. The complete blood cell count, serum electrolytes, and creatinine were normal. Surgical intervention was not recommended. The patient received another 2 cycles of chemotherapy. CT imaging after the final chemotherapy cycle showed that PI had improved.

Case 4

A previously healthy 46-year-old man was diagnosed with Philadelphia chromosome positive acute lymphoblastic leukaemia. The WBC count was elevated to 42.2 $\times$ 10^9/L and consisted mostly of lymphoblasts. Induction chemotherapy with cytotoxic agents and steroids was initiated. The tki imatinib 600 mg/d was added for the Philadelphia chromosome positive disease status [6]. Twelve days later, the patient presented with neutropenic sepsis, which required intravenous antibiotics, fluids, and vasopressors. Chemotherapy agents, including imatinib, were discontinued. The next day, the patient required tracheal intubation and mechanical ventilation. Five days later, abdominal distention was noted. A plain abdominal roentgenogram (Figure 4A)

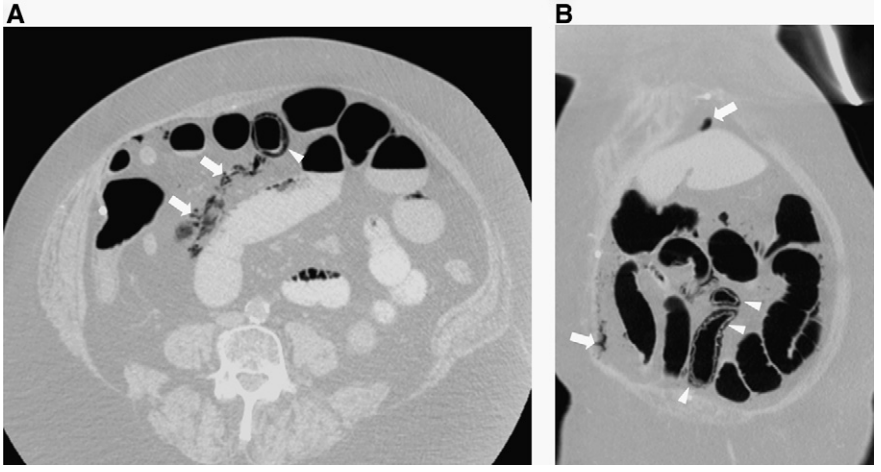

Figure 2. Incidental detection of pneumatosis intestinalis in a patient treated with the tyrosine kinase inhibitor sunitinib for recurrent renal cell carcinoma. (A) Axial computed tomographic abdominal images, showing evidence of air within the small bowel wall (arrowhead). The air dissects through the walls into the adjacent mesentery (arrows). Note normal adjacent air and contrast-filled bowel loops. (B) The coronal computed tomography images, showing pneumatosis intestinalis (arrowheads) and free intraperitoneal air (arrows).

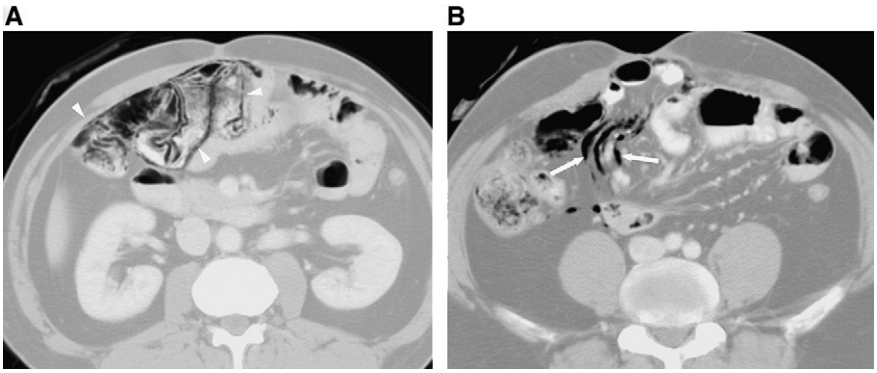

Figure 3. Incidental detection of pneumatosis intestinalis in a patient receiving systemic chemotherapy for enteropathy-associated T-cell non-Hodgkin lymphoma. (A) Axial computed tomographic (CT) images of the mid abdomen, demonstrating extensive pneumatosis intestinalis (arrowheads) within multiple loops of small bowel. (B) An inferior-section CT image, showing air tracking along the mesenteric vessels (arrows).

revealed dilatation and PI within the small bowel and ascending colon, and lucencies over the liver were consistent with portal venous gas. CT imaging confirmed PI throughout the small bowel and stomach, and gas within the portal venous system, along with dilatation of the jejunum and transverse colon (Figure 4, B and C). Blood cultures grew *Escherichia coli*. The patient's condition improved without surgical intervention. Imatinib and systemic chemotherapy were later resumed without recurrence of PI.

Discussion

The detection of PI in the midst of cancer treatment is difficult to interpret. An early classification system that groups PI by the mechanism of bowel-wall disruption does not account for its multifactorial nature in the setting of systemic cancer treatments and does not guide clinical care [1]. The radiologic features of PI are variable and often of limited help in guiding clinical care. For instance, multiple submucosal and/or subserosal circular cysts are benign findings, often limited to the colon, known as pneumatosis cystoides intestinalis (PCI) [7–9]. Linear distribution of gas within the bowel wall is a nonspecific finding seen in benign and life-threatening presentations of PI [9,10]. The presence of hepatic portal gas and PI implies gastrointestinal necrosis that is often associated with life-threatening clinical scenarios [11].

More recently, Ho et al [10] classified PI to either benign or life-threatening clinical presentations and accounts for the multifactorial nature of PI seen with systemic cancer treatments. This classification places benign presentations of PI into 8 categories: (i) pulmonary diseases that predispose to alveolar rupture; (ii) iatrogenic causes; (iii) systemic disorders, including vasculitis; (iv) hemoglobin disorders; (v) intestinal disorders that inhibit mucosal defenses or disrupt motility; (vi) medications, including steroids and chemotherapy agents; (vii) solid organ and bone marrow transplantation related infections; and (viii) idiopathic primary pneumatosis and PCI. Life-threatening presentations of PI include intestinal ischemia, severe infections, including *Clostridium septicum*, direct intestinal trauma, and bone marrow transplantation and solid organ transplant-related complications.

The first 3 scenarios represent benign presentations of PI, and the fourth case manifested in a life-threatening manner. The radiologic features are summarized in Table 1. In the first case scenario, it is likely PI was related to the tki imatinib. The linear gas pattern and melena excluded PCI. Infectious agents within the bowel were excluded. Abdominal pain and melena in immunocompromised hosts is suggestive of *C septicum* or cytomegalovirus infection. However, *C septicum* presents as life-threatening colitis in

Table 1
Summary of the radiologic findings seen in the 4 cases of PI[a]

Case no. (Figure no.)	Plain film radiographs	CT images	Follow-up imaging
1 (1)	PI without free intra-abdominal air	PI in the ascending and transverse colon with extraluminal gas	Radiographs 2 wk later showed decrease in PI
2 (2)	No examination	PI within the distal small bowel and free intraperitoneal air	CT 4 mo later showed absence of PI
3 (3)	No examination	Extensive PI in distal small bowel and extraluminal air	PI reduced even when chemotherapy was continued
4 (4)	Dilatation and PI that involve the small bowel and portal venous gas	PI that involves stomach and small bowel and presence of portal venous gas	PI resolved without surgical intervention

CT = computed tomography; PI = pneumatosis intestinalis.

[a] All CT examinations were completed on a GE 64-slice volume CT Lightspeed scanner (GE Medical Systems, Milwaukee, WI); the images are acquired as single, venous-phase, standard-axial, abdominal CT protocol with oral and intravenous contrast; coronal reformats were obtained from axial images; slice thickness was 2.5 mm; when used, the CT contrast agent was Omnipaque 300 mg/mL (GE Healthcare, Princeton, NJ).

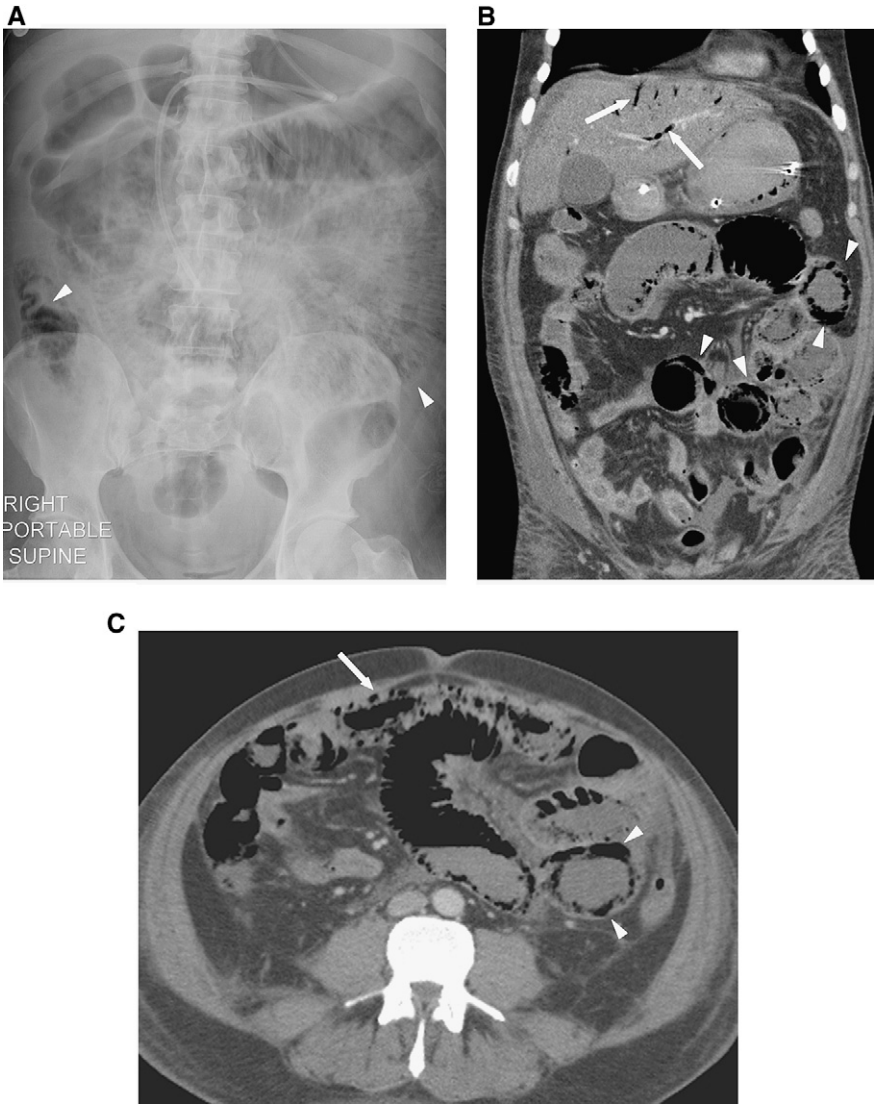

Figure 4. Pneumatosis intestinalis in a patient with Philadelphia chromosome positive acute lymphoblastic leukaemia that presented with febrile neutropenia during induction chemotherapy that included the tyrosine kinase inhibitor imatinib. (A) A plain radiograph of the abdomen, revealing multiple loops of small bowel with linear streaks of air in keeping with bowel pneumatosis (arrowheads). (B) Coronal computed tomographic (CT) abdominal images, depicting pneumatosis intestinalis (arrowheads) and air in the portal venous system (arrows). (C) The axial CT image, revealing pneumatosis intestinalis (arrowheads) with air fissuring through to the serosal surface of bowel wall (arrow).

neutropenic hosts, which was not found in this scenario [12,13]. Serologic tests excluded cytomegalovirus infection. PI has not been described in the setting of β-thalassemia trait, a known diagnosis in this patient, but has manifested in the setting of more-severe hemoglobin disorders [14,15]. There is a single report of PI in a patient with CML that only manifested during cytotoxic chemotherapy treatment [16].

Imatinib could potentially cause PI through non-neutropenic immunosuppressive effects and/or inhibition of intestinal motility. For instance, imatinib disrupts normal maturation and antigen presentation capabilities of dendritic cells, and inhibits T-cell proliferation and function [17]. Imatinib also disrupts normal colonic motility through inhibition of the KIT receptor [18–20].

The second scenario involves PI detected incidentally during treatment with the tki sunitinib for recurrent RCC. The patient was known to have chronic obstructive pulmonary disease, which is also associated with benign presentations of PI. However, sunitinib has been associated with PI [3]. The plausible mechanism is inhibition of vascular endothelial growth factor receptors and subsequent impairment of the regenerative ability of the intestinal mucosa to repair microperforations [21].

In the third case, PI developed in an asymptomatic patient during chemotherapy for NHL. PI was not related to the prior abdominal surgery, given the prolonged time interval, and PI was not seen on earlier postoperative CT imaging. PI could have been related to the cytotoxic chemotherapy agents that damage intestinal mucosa and/or the high doses of steroids that increase permeability through the bowel wall by depletion of lymphoid tissue in Peyer patches [1,22]. Despite the extensive PI, the non–life-threatening presentation is

consistent with Ho et al [10], in which PI is considered as a benign clinical presentation when solely related to systemic chemotherapies.

The fourth case underscores the complexity in assigning PI to a single mechanism in the setting of systemic cancer treatments. The presence of portal venous gas, however, is considered an ominous radiologic abnormality that is often associated with bowel necrosis, and its presence was in keeping with the life-threatening presentation in this patient [11]. Mechanical ventilation used to mange the patient's hypoxia could have predisposed to PI through alveolar rupture. The cytotoxic chemotherapy agents and steroids used for acute lymphoblastic leukaemia treatment were other potential causes of PI. However, these tend to be associated with benign presentations of PI, which is not consistent with this patient's presentation. Causes of PI listed by Ho et al [10] that could account for this life-threatening presentation include neutropenic colitis or intestinal ischemia related to hypotension and the use of vasopressor agents. The patient was receiving treatment with the tki agent imatinib at the time of presentation and was considered a potential contributing factor. This patient had at least 6 identifiable conditions known to manifest as PI; this underscores the importance of classifying PI by clinical presentation.

An interesting finding is that 3 of the 4 patients who presented developed PI while receiving tki agents. The strongest association is with the first case, in which all other causes of PI were excluded. The other 2 cases presented with other conditions that predispose to PI. However, the tki agents cannot be completely dismissed, given that other unexpected adverse effects have emerged with this class of anticancer agents since coming to market [3,23,24]. These cases stress the need for ongoing vigilance for undocumented adverse effects when using novel therapies and underscore the complexity of PI when it develops during systemic cancer therapy.

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